ABSTRACT

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ION PAIRS IN THE REARRANGEMENT OF THE CUBYLCARBINYL SYSTEM

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Mechanistic information has been obtained for the Wagner-Meerwein rearrangement of cubylcarbinyl-p-nitrobenzoate from kinetic data gained using lithium perchlorate as added salt. Further attempts have been made to describe the rearrangement of cubylcarbinol using various concentrations of perchloric acid. The rate of rearrangement in this solvent has been shown to be comparable to that when aqueous hydrogen bromide is solvent.

ION PAIRS IN THE REARRANGEMENT OF THE CUBYLCARBINYL SYSTEM

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R= iv T = 20

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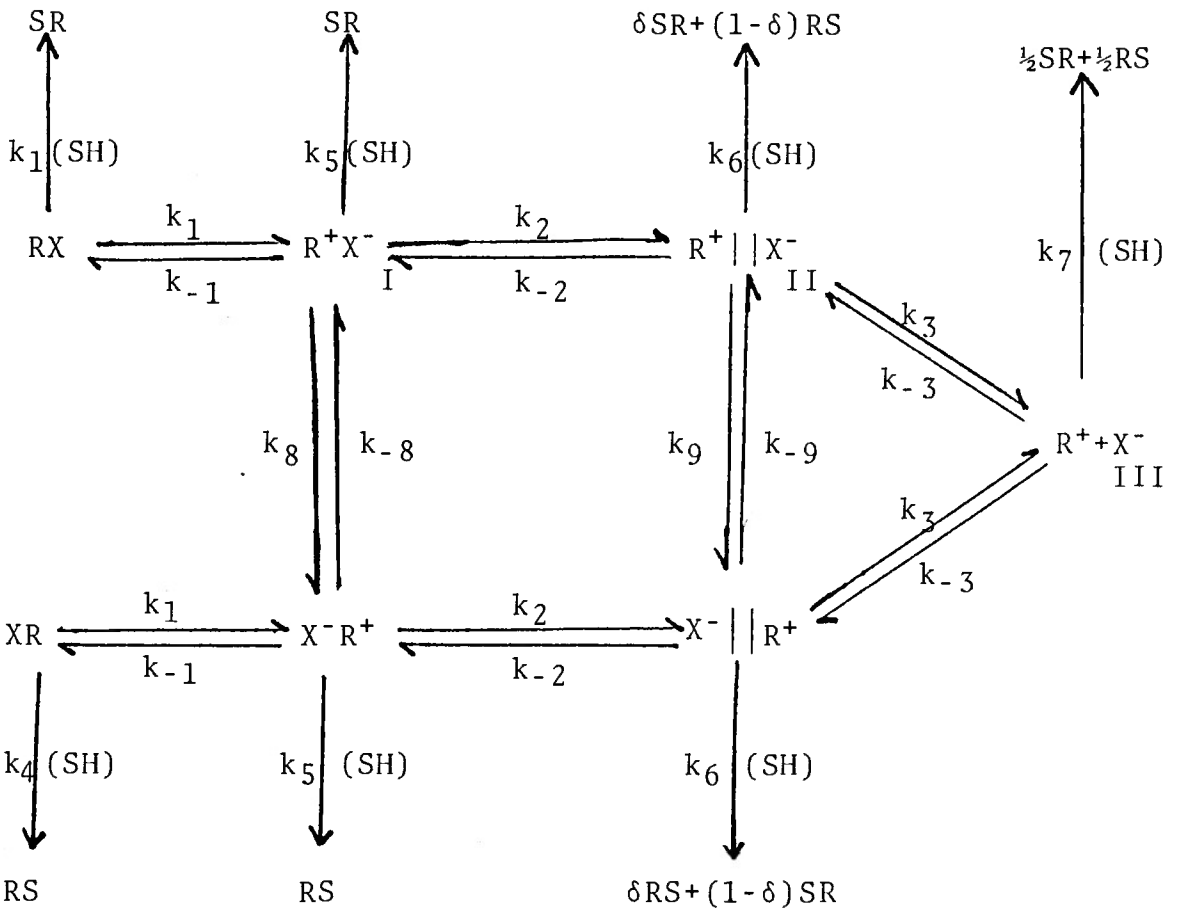
INTRODUCTION

Ionization of organic halides and esters is a complex process involving several intermediates. In many cases, the steps involved in forming these intermediates are reversible. Shiner[1] has proposed the following scheme for solvolytic reactions of this type:



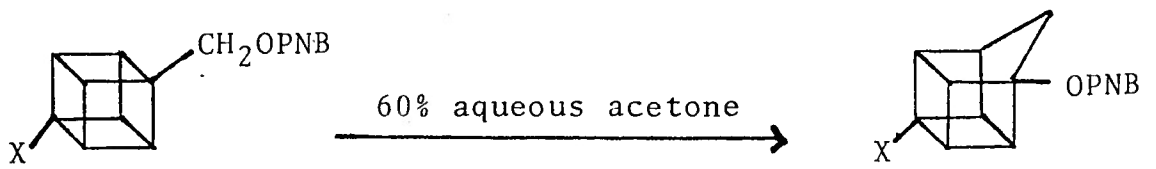
In this scheme, the solvent assists in the breaking of the R—X bond to form, initially, an intimate ion pair (I) in which the gegen ions are jointly surrounded and stabilized by an envelope of solvent molecules. This may be succeeded by a less close, solvent-separated ion pair (II) in which a solvent molecule(s) now separates the constituents. The final state (III) is one in which the constituents of the ion pair are completely dissociated, each now being surrounded and stabilized by its own envelope of solvent molecules. Attack on R^+ by a nucleophile present in the solution or, preferentially, by the more numerous and closely associated solvent molecules, if these are suitable, can take place at any stage along this sequence. The more stable the carbonium ion, however, the less likely it is to be attacked, and the further along the sequence it is thus expected to persist. In this formulation, SR represents the enantiomeric configuration to RS, etc. In the ion pairs, it is assumed that a solvent molecule is present at the backside of R^+.

Ion pair return, i.e., the recombination of ions from an ion pair to form a covalent bond, (k_{-1}), has been at the center of many recent investigations.[2,3] After careful observations, Winstein and Robinson[4] concluded that the best working hypothesis of the importance of ion pair return is that two kinds of ion pairs, i.e., intimate and solvent-separated, are discrete intermediates in solvolysis, and that these respond differently to an added salt. The solvent-separated ion pair is presumed

to be much more reactive than the intimate ion pair toward added lithium perchlorate. The special salt is one such as lithium perchlorate, which causes a rapid, non-linear increase in the rate for low salt concentrations, followed by a linear increase in rate constant with the increased concentration of added salt. In an effort to illustrate the special salt effect on the titrimetric acetolysis rate of threo-p-anisyl-2-butyl-p-bromobenzenesulfonate, Winstein and Fainberg[5] determined the rates of solvolysis at six concentrations of lithium perchlorate. Their results showed that an increase in lithium perchlorate concentrations produces a corresponding increase in rate constant. At very low concentrations, the increase is accelerated and non-linear.

The special salt effect is one of the methods for studying carbonium ion reactions that has gained in utility over the last several years. One very interesting carbonium ion reaction, rearrangement of the cubylcarbinyl system, has afforded some information that merits further investigation. First, esters of this system have been shown to undergo Wagner-Meerwein rearrangement under solvolytic conditions to give the less strained homocubyl ester with greater than 95 percent internal return of the leaving group.[6] In an earlier study, Dauben et al. investigated the solvolysis of bicyclo[2.2.0]-hexane-1-methyl-p-nitrobenzoate,[3] which also rearranges with excessive internal return of the leaving group. Using a series of strained, neopentyl-type esters containing no unusual

electronic properties, Dauben obtained a very good correlation between relative rates of solvolysis vs. strain release.[3] This consistency of relationship was interpreted as evidence for anchimeric assistance. Further, since relief of strain energy during ionization would complement the energy gained in forming a tertiary carbonium ion, and an increase in strain energy during ionization would reduce the net gained in forming a tertiary carbonium ion, the results suggest the concept of a concerted ionization-rearrangement with anchimeric assistance. The high degree of internal return in the rearrangement of cubylcarbinyl-p-nitrobenzoate suggests the possibility that this reaction never proceeds to the solvent separated stage where solvent molecules will then be in direct competition with the p-nitrobenzoate group for pairing with the alkyl moiety.



1 X = H

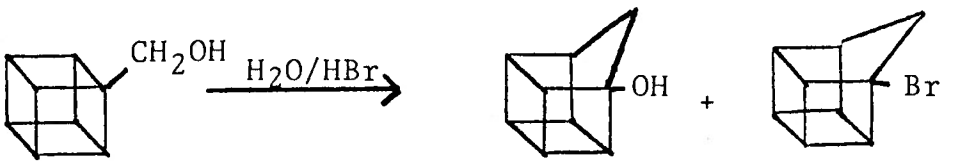
2 X ≠ H

3 X = H

4 X ≠ H

The same general results were obtained in the acid catalyzed rearrangement of cubylcarbinol (5).[2] Reaction of cubylcarbinol with 48% aqueous hydrogen bromide affords 1-homocubyl alcohol (6) and 1-homocubyl bromide (7) in a ratio of 2:1 respectively. While all the usual effects, e.g., solvent substituent effects,

etc., are operative, they seem to have no effect on the product ratios.



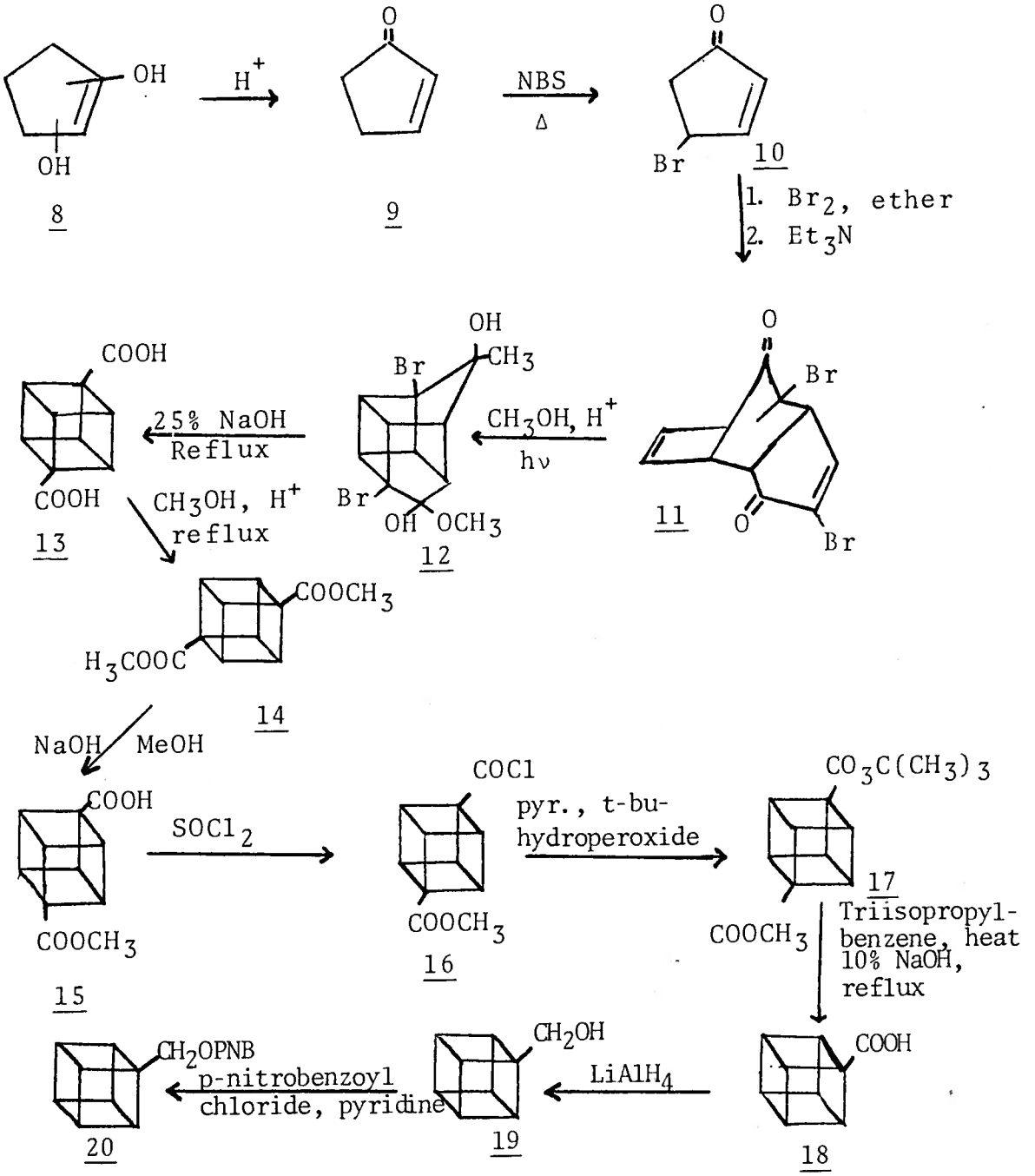
5 6 7

2 : 1

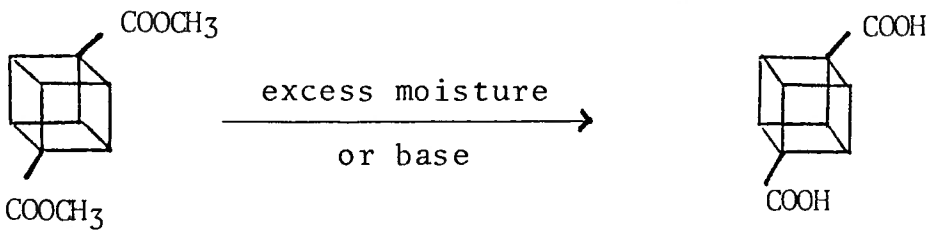
In order to make further mechanistic determinations of these rearrangements in the cubylcarbinyl series, specific experiments were designed to examine the effect of lithium perchlorate for a possible salt effect and the intervention of ion pairs in the cubylcarbinyl-p-nitrobenzoate rearrangement. Other reactions planned were for the reinvestigation of the product ratio in the rearrangement of cubylcarbinol, and attempts to determine the extent and rate of rearrangement of this alcohol in non-nucleophilic solvents.

RESULTS AND DISCUSSION

The cubane derivatives needed for this work were prepared according to the following scheme:[7]



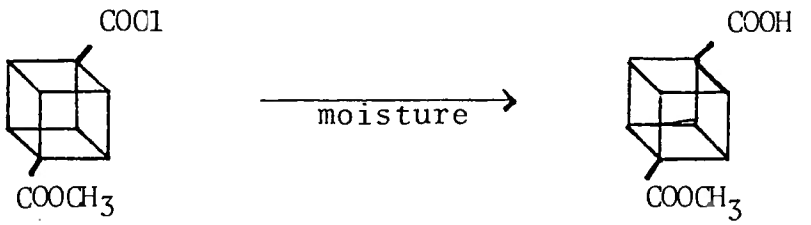
Most of these steps are simple reactions and can be accomplished without difficulty; however, precautionary measures should be discussed for several of them. Fortunately, it is not necessary to stop and meticulously purify every intermediate to effect a reasonably good yield of the ensuing intermediate or product. The step, 14⟶15, however, is one where this necessity does exist. This step is so sensitive to conditions that if any moisture is allowed to reach the reaction flask, complete hydrolysis occurs and one has to go back two steps to cubanedicarboxylic acid (13), repeat the esterification and hydrolysis, and absorb excess losses inherent in the increased number of steps. Excess losses also result if one fails to obtain pure 14. The inclusion of anything foreign in the weight will cause inaccurate use of base, and complete hydrolysis as a consequence.



14 15

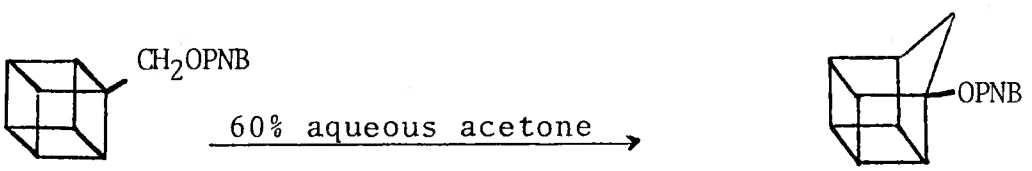
Another mistake that can be made is in the preparation of the acid chloride 16. Again, an obvious sensitivity to moisture exists. Therefore, one has to be very careful in

preparing the thionyl chloride to insure that no moisture enters the reaction flask. Once the acid chloride is prepared, it is necessary to maintain completely anhydrous conditions. This may even necessitate the employment of a drying tube on the aspirator line during removal of the excess thionyl chloride.



16 15

Cubylcarbinyl-p-nitrobenzoate was solvolyzed in unbuffered 60 percent aqueous acetone in an effort to duplicate previously reported data and thereby obtain a reasonable standard. Least squares analysis of the kinetic data gave a fairly good first order rate constant of $2.45 \times 10^{-6} sec^{-1}$. The reaction was repeated under identical conditions but with 0.1M added lithium perchlorate. The results (see table) show that the second run very nearly duplicated the first.



1 3

Table 1. First Order Rate Constants in 60% Aqueous Acetone (Rearrangement)

Cubylcarbinyl-p-nitrobenzoate	$kx10^6$ sec^{-1}	temp^o
Without added perchlorate	2.45	100 ± 1^o
Without added perchlorate	3.00[a]	100 ± 0.4^o
Without added perchlorate	7.50[b]	100 ± 1^o
With added perchlorate	2.38	100 ± 1^o
Rate in buffered trifluoroacetic acid	$3.6x10^{-4}$	38 ± 1^o

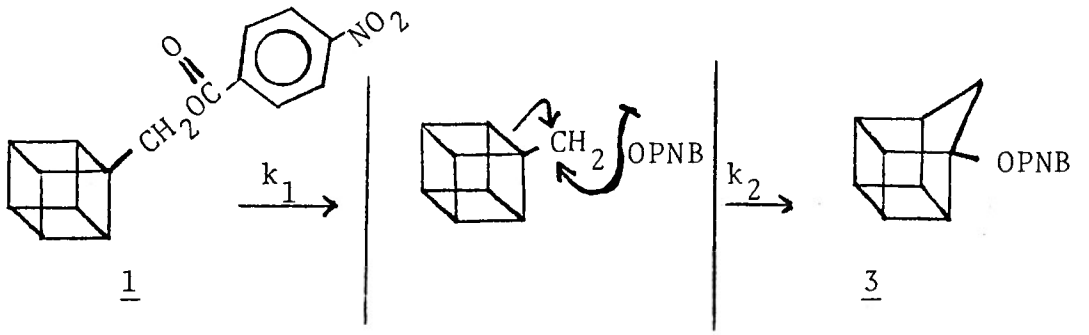
[a] Reference 6
[b] Reference 8

The method used in gathering the foregoing data and the reasoning employed is the same as previously reported.[6] The overall rearrangement rate was determined since the internal return product was produced in greater than 95 percent yield, and the first order rate constant for each run was determined by comparing the nuclear magnetic resonance integrals of the cubane cage protons (singlet, δ = 4.00) to that of the homocubane cage protons (multiplet, δ = 3.01-3.51).

Cubylcarbinyl-p-nitrobenzoate also solvolyzed in 60 percent aqueous acetone but with added sodium azide in excess. No attempts were made to monitor the rearrangement rate but the product was tested for the possible inclusion of alkyl azides. Infrared spectroscopy was utilized as a means of determining whether any azide product was produced. Since the infrared stretching vibration occurs at 2140 cm^{-1} for the azide group, it was quickly discerned that there was no azide product present. Also, analysis of the nmr spectrum revealed that only internal return product resulted from this reaction since the number of aromatic protons remained constant at four compared to seven for the cage protons of cubane plus homocubane.

The choice of 0.1M lithium perchlorate was based on the results of Winstein.[5] This reaction should show a significant increase in reaction rate over a standard run without lithium perchlorate if the reaction proceeds as far as the solvent separated stage before rearrangement. Results (see table) show that there was no rate increase upon the addition of

perchlorate. This indicated that the solvent separated stage was never attained since lithium perchlorate promotes solvolysis if solvent separated ion pairs are involved. Thus, it is highly probable that an ionization-rearrangement occurred, followed by internal return via two irreversible steps where $k_2 > k_1$.

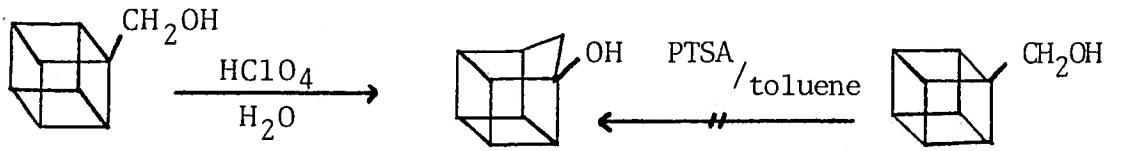


1 3

An equally interesting point was made by Harris and Raber[9] when they suggested that with the increasing stability of the substrate cation, there will be a corresponding increase in the degree of azide incorporation if azide ions are added. While the development of a planar carbonium ion does not occur, there should be a significant amount of azide product formed due to attack by the azide ion on the positively charged moiety of the ion pair resulting from the cubylcarbinyl-p-nitrobenzoate in solvent. This also assumes the presence of solvolysis product in the absence of azide ions. Since no azide was formed, this would suggest that the rearrangement occurred from the tight ion pair since if the solvent separated stage had been reached, there should have been some azide product formed. In an effort to determine whether a buffer would have any effect on the rate

of rearrangement of cubylcarbinyl-p-nitrobenzoates, the ester was rearranged in buffered trifluoroacetic acid for comparison with McEwen's results.[6] The rate (see table) was comparable to that reported for unbuffered conditions.

In order to assess the extent of rearrangement of cubylcarbinol in a non-nucleophilic solvent, cubylcarbinol was treated with several concentrations of perchloric acid. The alcohol 5 completely rearranges after one hour in 50 percent perchloric acid. After rearrangement was complete, the product was analyzed by nmr and infrared spectroscopy. The product, homocubyl alcohol, was confirmed by the multiplet at δ = 3.0-3.5 ppm, the doublet at δ = 1.9 ppm, and the discrete stretching band at 3400 cm^{-1}. This reaction was repeated at 35 percent perchloric acid with 70 percent rearrangement. However, when the concentration of perchloric acid was decreased to 10 or 20 percent, the rearrangement occurred too slowly to detect anything other than starting material. For the same purpose, cubylcarbinol was refluxed in toluene/p-toluenesulfonic acid for an extended period of time; however, no rearrangement was observed. After workup, followed by nmr and infrared spectral analysis, starting material was recovered unchanged. This reaction medium, not being a highly ionized solvent such as the aqueous mineral acid solutions, does not catalyze this reaction even at high temperatures.



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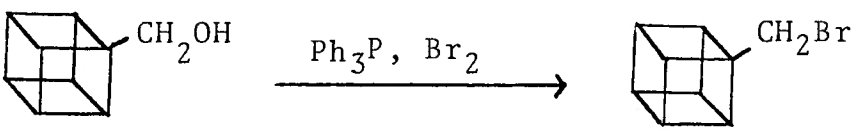
Although actual rearrangement rate constants for the rearrangement of cubylcarbinol (5) in HBr/H_2O or aqueous perchloric acid are unavailable, something can be said regarding the relative rates of these two reactions. The results obtained showed that the two rates are comparable when the concentrations are equal. This seems reasonable, since the leveling effect exerted on the two acids in aqueous media makes it difficult to differentiate between the two.

Attempts were made to prepare cubylcarbinyl bromide, making use of the following reaction conditions which promote substitution in neopentyl type compounds without rearrangement.



5

Unfortunately, repeated attempts to prepare cubylcarbinyl bromide by this method were consistently unsuccessful.

In light of the information gained from these experiments, it seems appropriate that a more definitive statement should be made concerning the ion pair involvement in some of the cubylcarbinyl rearrangements. For the rearrangement of the p-nitrobenzoate ester of cubylcarbinol, evidence has shown that the reaction never proceeds beyond the tight ion pair. In view of Dauben's[3] correlation showing the consistency of relationship between strain relief and rate as possible evidence of a concerted mechanism, it is highly conceivable that the mechanism of this reaction is a concerted ionization-rearrangement followed by a fast ion pair return. In the cubylcarbinol rearrangement, due to the slightly weaker nucleophilicity of H_2O compared to Br^-, there is probably some escape of ion pair to the solvent separated stage during rearrangement, and the Br^- then competes for the cation. The origin of the constant 2:1 ratio of alcohol to bromide in the rearrangement of cubylcarbinol is still unknown.

EXPERIMENTAL

Infrared (ir) spectra were recorded on a Beckman 4240 spectrophotometer, and unless otherwise specified, carbon tetrachloride was used as the solvent. Only the most prominent absorption bands in the spectra are listed. Nuclear magnetic resonance (nmr) spectra were taken on a Varian Associates A60-A spectrometer using carbon tetrachloride or deuteriochloroform solutions. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected.

Removal of solvent *in vacuo* or at the flash evaporator refers to evaporation using an all glass Buchler rotary evaporator.

Solvolysis of Cubylcarbinyl-p-nitrobenzoate in Trifluoroacetic Acid.--Cubylcarbinyl-*p*-nitrobenzoate (25 mg) was dissolved in 0.5 ml of purified (distilled from sodium trifluoroacetate) trifluoroacetic acid. The solution was sealed in an nmr tube. The tube was then placed in the sample probe of the spectrometer, maintained at 38°. After 10 min, 40 min, 70 min, and 100 min, nmr spectra were taken and the percent rearrangement determined by comparing the height of the integral for the cubane cage protons (δ = 4.0 ppm) to that for the homocubane cage protons (δ = 3.2 - 3.8 ppm). After the final spectrum, the solution was extracted 3 times

with anhydrous ether. The ethereal solution was washed once each with 5% aqueous sodium bicarbonate, 3% hydrochloric acid, water, and saturated brine. The solution was dried over sodium sulfate and concentrated *in vacuo*. An nmr spectrum was taken of the product and the percent internal return was determined by comparing the integral of the homocubane cage protons (δ = 3.2 - 3.8 ppm) to that of the *p*-nitrobenzoate protons (δ = 8.3 ppm).

Solvolysis of Cubylcarbinyl-p-nitrobenzoate in Buffered Trifluoroacetic Acid.--Cubylcarbinyl-*p*-nitrobenzoate (25 mg) was dissolved in 0.5 ml of trifluoracetic acid. Sodium triflouroacetate (11 mg) was added and the mixture was transferred to an nmr tube. After 10 min, 40 min, 70 min, and 100 min in the nmr probe, spectra were taken and the percent rearrangement was determined by comparing the height of the integral for the cubane cage protons (δ = 4.0 ppm) to that of the homocubane cage protons (δ = 3.2 - 3.8 ppm). The mixture was extracted 3 times with ether and the ethereal solution was washed once each with 5% aqueous sodium bicarbonate, 3% hydrochloric acid, water, and saturated brine. The ethereal solution was dried over sodium sulfate and concentrated *in vacuo*. The percent internal return was determined by comparing the height of the integral for the homocubane cage protons (δ = 3.2 - 3.8 ppm) to that for the *p*-nitrobenzoate protons (δ = 8.3 ppm).

Solvolysis of Cubylcarbinol in Perchloric Acid.-- Cubylcarbinol (25 mg) was added to 10 ml of a 50 vol percent

solution of perchloric acid and shaken vigorously. The reaction was allowed to go for 1 hr, then diluted with 3% sodium bicarbonate and extracted with ether. The extract was washed once each with water and saturated brine. After drying over sodium sulfate, the ether was removed by rotary evaporation. The resulting white crystalline substance was analyzed by nmr and ir spectroscopy. The moderately intense but discrete stretching band at 3400 cm^{-1} confirmed an alcohol and the nmr spectrum revealed that the cubane system (singlet at δ = 3.8 ppm) had rearranged to the homocubane system (multiplet at δ = 3.0 - 3.7 ppm and doublet at δ = 1.9 ppm). This procedure was repeated using 10%, 20%, and 35% $HClO_4$.

Reaction of Cubylcarbinol with Toluene/p-toluenesulfonic Acid.--Cubylcarbinol (25 mg) was dissolved in 10 ml of toluene. p-Toluenesulfonic acid (34 mg) was added and the mixture was refluxed for 3 hrs. The cooled solution was extracted 3 times with ether and the ether extract was washed once each and in order with 5% aqueous sodium bicarbonate, water, and saturated brine. The ether layer was then dried over sodium sulfate, then concentrated in vacuo. The residue was recrystallized from n-hexane and analyzed by nmr and ir spectroscopy.

Attempted Preparation of Cubylcarbinyl Bromide.--Cubylcarbinol (50 mg) was mixed with 970 mg of dry triphenylphosphine in 10 ml of dimethyl formamide (DMF) under a nitrogen atmosphere. Fisher "purified" bromine was added over a 15 min period while the flask temperature was

maintained below 55°. The addition was stopped when a few drops persisted in giving the solution an orange tint. The most volatile material was removed by distillation at 5 mm into a receiver cooled in a Dry Ice bath. Cold water was added, but no separation occurred. The mixture was then extracted 3 times with ether and the extract was dried over sodium sulfate. The ether was then evaporated and an ir spectrum was taken of the residue. Analysis of the spectrum revealed that the alcohol still remained, indicating that bromination never took place. This bromination was attempted using acetonitrile at 0° as solvent. After bromination of the triphenylphosphine, the acetonitrile was evaporated off. DMF was added, followed by the cubylcarbinol. Subsequent workup was the same as above with the same result.

Solvolysis of cubylcarbinol in DBr/D_2O.--Cubylcarbinol (25 mg) was dissolved in 0.5 ml of 23.5% deuterium bromide in deuterium oxide. The mixture was transferred to an nmr tube and the tube was inserted into the sample probe of the spectrometer. Spectra were taken as frequently as possible, but it became evident that this rearrangement was too facile at 38° to continuously monitor by nmr.

Solvolysis of Cubylcarbinyl-p-nitrobenzoate in 60% Aqueous Acetone with Added Azide Ions.--Cubylcarbinyl-p-nitrobenzoate (25 mg) was dissolved in 6.5 ml of a 60 vol percent aqueous acetone solution. Sodium azide (24 mg) was added. The mixture was degassed and sealed in a reinforced pressure tube at Dry Ice-methanol temperature and placed in

an oil bath maintained at 100° ± 1°. After 40 hrs, 94 hrs, and 120 hrs, a single tube was removed and opened. The contents of the tubes were transferred to a round bottom flask and the acetone was removed by rotary evaporation. The aqueous residue was extracted 3 times with ether. The ethereal portions were combined and washed once each with 5% sodium bicarbonate, 3% hydrochloric acid, water, and saturated brine. After drying over sodium sulfate, the solvent was removed by rotary evaporation. The residue was recrystallized from n-hexane and analyzed by nmr spectroscopy.

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